REMARKS

Claims 13-29, 34, 36, and 42-51 remain pending in the application. Claims 13, 36, 42, and 49-51 are amended to clarify their scope and to correct typographical errors. No new matter has been added.

Information Disclosure Statement

Applicant submits herewith an Information Disclosure Statement.

Rejections for Obviousness-type Double Patenting

The Office action mailed October 18, 2008 (the "Office action"), notes that the obviousness-type double-patenting rejection over copending U.S. Patent Application No. 09/367,950 is maintained, as no terminal disclaimer has yet been filed. Claims 13-15, 17, 19, 20, 22-25, 30-36, 38 and 42 are said to be included in the rejection for obviousness-type double patenting (see page 4 of the Office action). Applicant notes that this rejection is apparently being applied to several claims that were previously canceled (and remain canceled) from the present application, i.e., claims 30-33, 35, and 38, as well as some but not all of the presently pending claims. Clarification of the precise claims being rejected on this ground is requested. For the record, applicant reiterates that a terminal disclaimer will be filed in one of the two applications if such is still deemed appropriate once the claims of one of the two applications are allowed.

Rejections under 35 USC § 103(a) for Obviousness

Claims 13-15, 17, 18, 20-29, 34, 36, and 42-51 were rejected as obvious over Carling et al., WO 9311773 A1 ("Carling"). Applicant traverses.

Carling teaches a composition containing a combination of two active agents, formoterol and budesonide, for use in treating asthma. As in previous Office actions in this case, the Office takes the position that Carling teaches that "the suitable daily dosage is up to 8 inhalation." The Office apparently derives the notion of "up to 8 inhalation" from Carling's teachings at page 6,

lines 32-24, that "a suitable daily dose of formoterol is in the range of 6 to 100 μg," combined with the various examples on pages 7-9 of Carling illustrating that an inhaler can deliver a single dose of formoterol as low as 12 μg, i.e., approximately 1/8 of the proposed 100 μg maximum daily dose of formoterol. The Office also points to the teaching at page 6 of Carling that the particular dose used "will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)," interpreting that to mean that the patient can decide for himself to take more than just two doses per day (up to a maximum of eight doses) if he is experiencing an acute asthmatic attack (see the Office action at page 9). Applicant submits that this is simply not a reasonable interpretation of what Carling teaches.

Rather than teach that the patient can decide whether and how many doses to take on any given day, Carling explicitly states that the intended dosing regimen is twice per day. See, for example, the statement at page 4, lines 19-21, of Carling: "The combination according to [the] present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma" (emphasis added). Carling reiterates this at page 6, lines 22-23: "The intended dose regimen is a twice daily administration…." (emphasis added). In fact, the latter statement is the first part of the sentence on which the Office relies for the teaching "where the suitable daily dose of formoterol is in the range of 6 to 100 μg." To emphasize this point, Applicant reproduces the sentence here:

> The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 μg with a preferred dose of 6-48 μg and the suitable daily dose for budesonide is 50 to 4800 μg with a preferred dose of 100-1600 μg.

That sentence, read in its entirety, makes it clear that Carling is saying the intended *twice daily* administrations can provide a daily total of formoterol in the range from 6 to 100 μg, i.e., the total daily dose of 6 to 100 μg formoterol should be split into two administrations per day. The total daily dose is inextricably linked to the twice daily administration regime by the word "***where***", indicating Carling's intent to teach what range of dosage should be administered in the intended twice daily administration. The Office inexplicably ignores the directive in the first part of the sentence regarding "twice daily administration" in order to read into Carling a

nonexistent instruction to take any desired number of doses up to a maximum total daily dose of 100 μg, and to administer the doses however many times each day the patient desires to do so. As applicant noted in the prior Response filed July 27, 2007, those of skill in the art understood that budesonide should be administered only as a maintenance treatment, and no more than twice per day, consistent with applicant's reading of Carling.

Carling's statement at page 6, lines 27-29, that the particular dose used "will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)" does not in any way contradict Carling's teaching that the formoterol/budesonide combination should be administered in a set dosage just twice per day. These factors are listed by Carling because they are some of the factors that the physician considers when deciding what set daily dose to prescribe for a given patient. Obviously the patient would not be handed an inhaler and told to take any amount up to 100 μg of formoterol and up to 4800 μg budesonide he desires, based on his own perception of what a person of his weight, age, and disease condition should take. It is up to the physician to instruct the patient in this regard. A patient that frequently has severe bouts of acute asthma attacks may be prescribed a larger fixed twice-daily dose than that prescribed for a patient who reports only mild and infrequent episodes. There is no teaching in Carling that the patient should decide for himself when to increase or decrease the daily dosage, and certainly no teaching that extra doses should be administered whenever the patient feels an attack coming on.

The Examiner's confusion may stem from a belief that each "administration" can involve only a single "dose" delivered by the inhalers exemplified in Carling (e.g., 12 μg formoterol). In fact, when a physician needs to prescribe a total daily dose for a given patient that is relatively high (because of the patient's age, weight, and/or severity of disease), she can simply tell the patient to inhale two or three or four individual doses from the inhaler each morning and the same number each evening. Regardless of the number of doses inhaled at each of the two daily administrations, the number of daily administrations does not change. Nor does the total dose inhaled at each of the two daily administrations vary from day to day. The physician tells the patient exactly how many times per day to administer the combination (two) and the number of

inhalations (i.e., doses) per administration, and the patient is expected to follow this instruction to the letter. For example, if a physician decides, based on the age, weight, and general severity of disease of a given patient, that the patient should inhale an amount of Carling's formoterol/budesonide combination sufficient to deliver a total of 96 μg of formoterol each day, the patient could be given an inhaler as in Carling's Example 1 and be told to inhale, every day, four 12 μg doses at one administration (e.g., every morning) and four more 12 μg doses at the second administration (e.g., in the evening). The eight doses needed to deliver the prescribed amount of 96 μg per day from the Example 1 inhaler can thus be administered just twice per day, in accordance with Carling's teachings. There is no need to read into Carling a teaching that up to eight doses can be spread throughout the day and administered whenever the patient feels the need.

Applicant provided voluminous evidence in the Response filed July 27, 2007, that this is how Carling's teachings would have been understood in the art. Applicant also supplied with that previous Response extensive evidence of surprising results; long-felt, unsatisfied need; and skepticism of experts, all of which the Examiner found to be "not persuasive".[1] The comments on pages 12-23 of the present Office action are addressed below.

On page 13 of the Office action, the Examiner dismisses applicant's arguments regarding Exhibit 1, a 1997 copy of the product insert packaged with the budesonide inhaler branded as Pulmicort® Turbuhaler®, on the ground that "evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention." This is not understood. This evidence was submitted as a teaching away from the present invention, not as "unexpected results." Applicant asks the Examiner to re-read the arguments based on Exhibit 1 in the prior response, and to acknowledge that this constitutes a teaching-away from the present invention.

On pages 12-14 of the Office action, the Examiner dismisses the product insert evidence submitted as Exhibit 2 in the prior response, saying that the product insert teaches that the dosage should be adjusted to the severity of the disease. This teaching of course means that the physician should decide when an increase or decrease of the twice-daily administration is

[1] The reference to "131 Affidavits" on page 12 of the Office action is not understood. No such affidavits were filed with applicant's July 27, 2007 response. The evidence was filed as exhibits.

needed, and should instruct the patient accordingly. The Exhibit 2 product insert makes it clear that the patient cannot take more or less than the fixed dosage regimen without the physician's approval, and must seek medical attention if his dosage ever exceeds the exact amount the physician instructed him to take every day. The statement quoted in the Office action ("If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroids should be prescribed") is perfectly consistent with applicant's position. It is the physician who decides, not the patient. The patient is never, EVER allowed to take more or fewer daily doses of the Symbicort® combination product than what is prescribed, and never on an as-needed basis as determined by the patient. According to Exhibit 2, the Symbicort® combination product is used as a maintenance treatment only, not for relief of acute symptoms.

On page 16 of the Office action, the Examiner dismisses applicant's Exhibit 3 because "it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention." Applicant again reminds the Examiner that, as with Exhibit 1, this exhibit was submitted as evidence that the art taught away from the present invention, and not as "unexpected results." Applicant respectfully requests that the Examiner review Exhibit 3 and applicant's remarks regarding that exhibit in the prior Response, and acknowledge that Exhibit 3 teaches away from the present invention.

On pages 17-18 of the Office action, the Examiner dismisses applicant's evidence submitted as Exhibits 4 and 5 with the prior Response, noting that the controls in the clinical trials discussed in those Exhibits utilized not only budesonide and formoterol, but also terbutaline (a short-acting bronchodilator). The Examiner says that this means the evidence is not "commensurate in scope with the claimed invention." This is not understood. The experimental arm utilized a method exactly as claimed, so is unquestionably "commensurate in scope with the claimed invention." The terbutaline was supplied to the patients receiving only maintenance treatment, i.e., budesonide twice per day, or budesonide/formoterol twice per day. The patients who used the budesonide/formoterol combination both as maintenance treatment twice per day and as a reliever in case of worsening symptoms at any given time (i.e., using the

combination in accordance with the invention) actually did better than patients who received only maintenance treatment with the combination (i.e., in accordance with Carling's teachings) plus the terbutaline as a reliever. Though the Examiner is apparently concerned that the use of terbutaline in the control arms means that the experiment did not compare the claimed method to the closest prior art (i.e., Carling), in fact it did. The patients being treated with the budesonide/formoterol combination solely as a twice-daily maintenance treatment obviously would not have fared better had they been denied the use of terbutaline in case of emergencies. Thus, it is clear that applicant's methods work far better than what Carling taught. The Examiner's dismissal of this evidence is not warranted.

The Examiner makes a further point on page 19 of the Office action regarding the unexpected results in Exhibits 4 and 5, saying, "In order for the Applicant to show an unexpected result, there must be a difference in kind, rather than in degree between the Applicant's administration and the prior art." This would suggest that regardless of how much more effective a claimed treatment might be compared to closest prior art, the improved effect can never be considered "surprising results". This is not in accordance with law. See, e.g., *In re Corkill*, 711 F.2d 1496 (Fed. Cir. 1985): "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness…of the claims at issue." Applicant respectfully requests that the Examiner reconsider her position regarding the persuasiveness of applicant's unexpected results as described in the prior Response.

On page 21 of the Office action, the Examiner refers to Exhibit 5's comment that the mean number of additional doses taken from the combination inhaler (i.e., in addition to the two doses per day taken as maintenance therapy) was only one dose per day, and very few patients used high doses. The Examiner uses that comment as evidence that one reading Carling would know that additional doses could be safely taken. Applicant reminds the Examiner that Exhibits 4 and 5 are post-filing date publications, so were not available to one of ordinary skill prior to the present application's filing date. The new results reported in Exhibits 4 and 5 cannot be taken as evidence of what one of ordinary skill in the art would have understood upon reading Carling. Carling said to treat patients with just two administrations per day of the

budesonide/formoterol combination, consistent with what was known in the art regarding budesonide and formoterol treatment. There is no basis for reading applicant's method into Carling.

Withdrawal of the rejection for obviousness and allowance of the claims is respectfully requested.

The fees in the amount of $1050 for Petition for Three Month Extension of Time are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188002.

Respectfully submitted,

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